IN THE CLAIMS

1. (Currently Amended) A method of de novo designing molecules that bind to a receptor site on a protein comprising the steps of:

(a) building a molecule in the receptor site comprising: adding successive random molecular fragments to an initial molecular fragment that is loaded into the receptor site, estimating the free energy of the molecule being grown after each addition of a molecular fragment, and orienting each successive molecular fragment as it is added to the receptor site such that the free energy estimate for the molecule may be higher than a lowest free energy estimate possible for the molecule;

(b) repeating step (a) to generate a collection of molecules grown in the receptor site, and ranking the collection of molecules according to increasing free energy estimates to identify high-ranking molecules;

(c) selecting one or more functional groups of a high-ranking molecule identified in step (b) as a single restart fragment and using the restart fragment to build a second-generation of molecules according to steps (a) and (b);

(d) minimizing the energy of a protein/ligand complex comprising the receptor site and a second-generation molecule using an empirical force field;

(e) quantitatively measuring the empirical interaction energy of the second-generation molecules, and ranking the second-generation molecules, wherein a second-generation molecule of low interaction strength is ranked higher than a second-generation molecule of more negative interaction energy is ranked higher than a second-generation molecule of less negative or positive interaction energy;

(f) modifying high-ranking second-generation molecules from step (e) based on qualitative analysis of the second-generation molecules including determination of chemical viability, synthetic feasibility, solubility, and effect of the second-generation molecule on the structure of the protein, whereas such modification comprises: atomic and/or functional substitutions, initiating growth from a specific receptor site, inclusion of salt bridges or hydrogen bonds, and solubility-enhancing measures[.];

(g) repeating steps (c) through (f) until a second-generation molecule is built which is identified as high-ranking in both steps (e) and (f)[.]; and

(h) displaying at least one second-generation molecule built according to step (g).

2. (Original) The method of claim 1, wherein the receptor site is selected from the group consisting of: Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, and human carbonic anhydrase II protein.

3. (Original) The method of claim 1, wherein the empirical interaction energy comprises CHARMM interaction energy.

4. (Original) The method of claim 1, wherein the empirical force field comprises CHARMM.

5. (Cancelled).

6. (Cancelled).

7. (Cancelled).

8. (Cancelled).

9. (Cancelled).

10. (Cancelled).

11. (Cancelled).

12. (Cancelled).

13. (Cancelled).

14. (Cancelled).

15. (Cancelled).

16. (Cancelled).

17. (Cancelled).

18. (Cancelled).

19. (Cancelled).

20. (Cancelled).